

## II. REMARKS

Claims 17-36 are pending. Claims 18 and 19 are amended. No new matter is added.

### **Claim Objection**

Claims 34 and 35 are objected for reciting incorrect claim numbers. In response, Applicants renumber claims 35 and 36 as suggested by the Office.

### **Rejections under 35 U.S.C. § 102**

Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walker et al. 1994 (Walker), Pirttila et al. 1994 (Pirttila), WO01/62801, or Naslund et al. 1994 (Naslund). Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Solomon et al. 1996 (Solomon). Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(a) as alleged being anticipated by Huse et al. 2002 (Huse).

Applicants respectfully traverse. None of the cited references discloses each and every element of the claimed monoclonal antibody, which specifically binds to one or more epitopes present on the first 5 to 7 N-terminal amino acids of A $\beta$ 11-x polypeptide and does not specifically bind to a full length A $\beta$ 1-40/42 peptide.

It is well known in the art that various A $\beta$  peptides are present in diseased and normal aging brains, including the N-terminal truncated A $\beta$ 11-x and the full-length A $\beta$ 1-40/1-42 (A $\beta$ 1-40/42). As A $\beta$ 11-x peptides are the major species identified in the brains of patients with Alzheimer's disease (AD), it is important to specifically detect A $\beta$ 11-x without the cross-reactivity of A $\beta$ 1-40/42 for developing effective diagnosis and treatment for AD. See specification, page 2, lines 18-26, "*Recently, it was demonstrated that BACE-1 is the major  $\beta$ -secretase required for cleavage of APP at position +1 and that overexpression of BACE-1 results in an additional cleavage at the +11 site of the A $\beta$ , generating shorter A $\beta$ 11-40 and A $\beta$ 11-42 fragments, hereinafter also referred to as the A $\beta$ 11-x peptides. These A $\beta$  peptides have been detected in conditioned medium of primary rat neuronal cell cultures and mouse N2a cells, suggesting that they are normal APP cleavage products generated in neurons (3, 4, 5). Significantly, these shorter A $\beta$*

*fragments have also been identified as major species in AD brains and normal aging brains by biochemical analysis as well as Down syndrome brains with AD pathology by immunohistochemistry studies."* and lines 30-35, *"Despite the progress which has been made in understanding the underlying mechanisms of AD and other A $\beta$ -related diseases, there remains a need to develop methods and compositions for diagnosis and treatment of the disease(s). Thus, the ability to monitor cellular processing of the amyloid precursor protein would be of significant value in the diagnosis, prognosis, and therapeutic supervision of Alzheimer's disease."* Therefore, the present application provides the claimed antibody which (a) binds to one or more epitopes on the first 5-7 amino acids of A $\beta$ 11-x, (b) binds specifically to A $\beta$ 11-x, and (c) does not specifically bind to a full length A $\beta$ 1-40/42 peptide.

None of the prior art discloses a monoclonal antibody with all three of these characteristics. To illustrate the differences in the properties among the antibodies, Applicants submit the table below and discuss each antibody hereafter.

	Epitope of A $\beta$	Binds to A $\beta$ 11-x	Binds to A $\beta$ 1-40/42
Claimed antibodies	11-15/17 (first 5-7 amino acids of A $\beta$ 11-x)	Yes	No
10D5 (Walker)	3-6 (as evidenced by Frenkel)	Unknown	Yes
4G8 (Prittila, WO01/62891 and Huse)	17-24	Unknown	Yes
266 (WO01/62801)	17-25	Unknown	Yes
6E10 (Pirttila and Naslund)	4-9 (as evidenced by product description)	Unknown	Yes
AMY-33 (Solomon)	1-28	Unknown	Yes
6D/3D (Solomon)	8-17	Unknown	Yes
BAN50 (Huse)	1-10	Unknown	Yes
BNT77 (Huse)	11-16	Yes	Yes
BA27 (Huse)	Unknown	Unknown	Yes
BC05 (Huse)	Unknown	Unknown	Yes

As can be easily seen with reference to the table, all of the previously disclosed antibodies differ from the claimed antibodies in at least one way. All of the art-disclosed antibodies specifically bind to full-length A $\beta$ 1-40 and/or 1-42, in contrast to the claimed

antibodies. Some of the antibodies of the prior art also differ from the claimed antibodies in other ways, as discussed in detail below.

Walker discloses that the monoclonal antibody 10D5 binds to A $\beta$ 1-16 and native A $\beta$ . See page 377, right column, third paragraph, "*...we used monoclonal antibody (MAb) 10D5, a murine IgG, kappa light chain (whole IgG and/or Fab fragments) to amino acids 1-16 of A $\beta$ .*" and page 379, left column, fourth paragraph, " *$\beta$ -amyloid in untreated, fresh-frozen tissue sections was robustly labeled by antibody 10D5, whereas normal (non-A $\beta$ -immune) mouse IgG did not bind to native A $\beta$  in this tissue (data not shown).*" The antibody 10D5 is also disclosed by Frenkel et al. 1998, J.

Neuroimmunology 88: 85-90 (Frenkel); submitted previously. Frenkel states that 10D5 was obtained from Dr. D. Schenk, the senior author of Walker. See page 86, second paragraph, "*Monoclonal antibodies, 6C6 and 10D5, raised against soluble fragment of position 1-28 of  $\beta$ AP, were kindly provide by Dr. D. Schenk...*" Subsequent analysis in Frenkel indicates that 10D5 has a minimal epitope of A $\beta$ 3-6 and binds to A $\beta$ 1-40. See Frenkel, page 88, Abstract, "*The peptide EFRH inhibits binding of mAbs 6C6 or 10D5 to  $\beta$ -amyloid peptide in affinities identical to those obtained with the peptides corresponding to positions 1-9, 1-16 and 1-40 of [A] $\beta$ -peptide. These findings confirm that the peptide EFRH which is located at positions 3-6 within  $\beta$ -amyloid peptide represents the sequential epitope of mAbs 6C6 and 10D5.*" Accordingly, 10D5 binds to full-length A $\beta$ 1-40 at A $\beta$ 3-6. Further, 10D5 cannot not bind to A $\beta$ 11-x, since A $\beta$ 11-x does not contain the 10D5 binding epitope. Thus, 10D5, disclosed by Walker, differs from the claimed antibody in all three ways: the A $\beta$  epitope to which it binds, its lack of specificity for A $\beta$ 11-x and its specificity for full length A $\beta$ 1-40.

Pirttila discloses the monoclonal antibodies 4G8 and 6E10. 4G8 is also disclosed in WO01/62801; 6E10 is also disclosed in Naslund. The properties of these antibodies are discussed below.

WO01/62801 discloses that monoclonal antibodies 266 and 4G8 bind to full-length A $\beta$ 1-40/42; see Example 15, "*Using this method, the affinity of mouse antibody 266 for both A $\beta$ 1-40 and for A $\beta$ 1-42 was found to be 4pM. The affinity of 4G8 for A $\beta$ 1-40 was 23nM and for A $\beta$ 1-42 was 24nM.*" The binding epitope of 266 is identified to be A $\beta$ 17-25; see Example 16 of WO01/62801, "*the binding epitope for the mouse antibody*

266 appears to be between amino acids 17 and 25 of A $\beta$ . " Additionally, the binding epitope of 4G8 is identified as A $\beta$ 17-24 in Pirttila; see page 91, right column, fourth paragraph, *"The monoclonal antibody (mAb) 4G8 was specific to an epitope present on 17-24 amino acids of the A $\beta$ -peptide..."* Accordingly, 266 and 4G8 differ from the claimed antibody in at least two ways: the A $\beta$  epitope to which they bind and the specificity for full length A $\beta$ 1-40/42.

Naslund and Pirttila both disclose the monoclonal antibody 6E10 binds to A $\beta$  at amino acids 1-16. See Naslund, page 8379, left column, second paragraph, which discusses the SDS/PAGE immunoblot shown in Figure 2 of Naslund, and states that *"The membrane was . . . probed with monoclonal antibody 6E10 directed against residues 1-16 of A $\beta$ ."*; and Pirttila, page 91, right column, *"The monoclonal antibody (mAb) ...6E10 was raised to a peptide corresponding to the first 16 amino acid residues of A $\beta$  peptide."* Subsequent analysis indicates that the epitope of the 6E10 antibody is within A $\beta$ 4-9; see product prescription submitted previously. Naslund also discloses that this antibody binds to full-length A $\beta$ 1-40/42; see page 8380, Figure 2B, showing an SDS/PAGE analysis of crude hexafluoroisopropanol (HFIP) extract and purified monomeric A $\beta$ 1-40/42 with a molecular weight of 4 kDa which is identified by immunoblotting with 6E10. According to Naslund at page 8379, right column, first paragraph, *"[t]he indicated 4-kDa peptide (Fig. b) was identified as A $\beta$  peptide by N-terminal microsequencing."* Thus, 6E10 differs from the claimed antibody in at least two ways: the A $\beta$  epitope to which it binds (amino acids 4-9 vs. 11-15/17) and the specific binding to full length A $\beta$ 1-40/42.

Solomon discloses the monoclonal antibodies AMY-33 and 6F/3D, both of which bind to full-length A $\beta$ 1-40. See page 452, and right column, third paragraph, *"Synthetic  $\beta$ A4-(1-40) was obtained from Sigma...To determine the soluble  $\beta$ A4 the supernatants were then incubated for another 60 min with an excess of mAb AMY-33 and/or 6F/3D...to produce immunocomplexed  $\beta$ A4."* Thus, AMY-33 and 6F/3D differ from the claimed antibody in at least one way: specific binding to full-length A $\beta$ 1-40.

Huse discloses the monoclonal antibodies 4G8, BAN50, BNT77, BA27, and BC05. The differences between 4G8 and the claimed antibodies are discussed above. According to Huse, BAN50 recognizes A $\beta$ 1-10 and binds to A $\beta$ 1-40/42, BNT77

recognizes A $\beta$ 11-16 and binds to both A $\beta$ 1-40/42 and A $\beta$ 11-x, BA27 binds to A $\beta$ 1-40 and BC05 binds to A $\beta$ 1-42. See page 16279, left column, fourth paragraph "*mAbs BAN50 and BNT77, directed against amino acids 1-10 and 11-16 of A $\beta$ , respectively, were used as capturing antibodies. End-specific, horseradish peroxidase-conjugated mAbs BA27 (for A $\beta$ 40) and BC05 (for A $\beta$ 42) were then used for detection.*"; and page 16280, left column, first paragraph, "*BAN50 captures primary A $\beta$ 1-40 and A $\beta$ 1-42, whereas BNT77 detects N-terminally truncated species as well as full-length peptides.*" Thus, the antibodies disclosed in Huse all differ from the claimed antibody in at least one way: the specificity for full-length A $\beta$  peptides. Additionally, at least antibody 4G8 and BAN50 recognize a different epitope than the claimed antibodies.

Clearly, none of the antibodies in the cited documents have all three properties of the claimed antibody. Therefore, Walker, Pirttila, WO/0162801, Naslund, Solomon and Huse do not anticipate the monoclonal antibody recited in the claims.

With regard to the Office notion at page 6 that "*Applicant has provided no showing that the antibodies in the art have characteristics different from those specified by Applicant and do not in fact cross react with the full length of A $\beta$ -40/42 in the same titration or at the same concentration as those of the prior art. Applicant fails to provide side-by-side comparisons to demonstrate that the claimed antibody is different from those antibodies disclosed by Walker et al., Pirttila, WO0162801, Naslund and Huse*",

Applicants respectfully traverse. It is not necessary for Applicants to submit side by side data showing the claimed antibodies differ from the prior art, since the prior art teaches that the claimed antibodies have at least one characteristic which differs from the antibodies of the claims: namely, specific binding to full length A $\beta$ 1-40 and/or A $\beta$ 1-42. As can be seen in Fig. 2A, 2B and 2C of the captioned application showing data for a specific antibody of the claims, the claimed antibody does not bind to full length A $\beta$ 1-40, even at concentrations as high as 1000 ng/ml; yet it binds to A $\beta$ 11-x at a concentration as low as 0.1 ng/ml. The prior art teaches that all antibodies described therein specifically bind to A $\beta$ 1-40/42. The Office has not presented any reasoning to doubt the veracity of the statements in the art that the disclosed antibodies bind to full-length A $\beta$ 1-40/42; nor any reasoning to doubt the data in the specification showing specific binding to A $\beta$ 11-x,

and no specific binding to A $\beta$ 1-40. Thus, the claimed antibodies do, in fact, differ from the antibodies disclosed in the prior art, despite their structural similarity as antibodies.

Further, Applicants submit that the claimed monoclonal antibody has been utilized to specifically recognize A $\beta$ 11-x polypeptide by a person skilled in the art of Alzheimer's disease. This is evidenced by Liu et al. published in Acta Neuropathology 112: 163-174, titled 'Characterization of A $\beta$ 11-40/42 peptide deposition in Alzheimer's disease and young Down syndrome brains: implication of N-terminally truncated A $\beta$  species in the pathogenesis of Alzheimer's disease' submitted herein. In Liu et al., the monoclonal antibody M11 which corresponds to the claimed antibody is used to specifically detect the truncated A $\beta$ 11-40/42 peptide whereas the monoclonal antibodies 4G8, which is the antibody disclosed in Prittila, WO01/62891 and Huse is used to detect the full-length A $\beta$ 1-40/42 peptide. This is illustrated, for example, at page 165, left column, second paragraph states "*Antibodies: The following panel of antibodies was utilized to analyze different A $\beta$  species...monoclonal antibody (mAb) M11 (a gift from Jonson & Johnson/Janssens Pharmaceutica) specifically recognizes free A $\beta$ 11-40/42; mAb M266 (a gift from Eli Lilly) and 4G8 recognize total A $\beta$  (epitope 13-28 and 17-24 of A $\beta$ 11-x, respectively)*" and page 166, left column, second paragraph to right column, first paragraph states "*Characterization of free A $\beta$ 11-40/42 specific antibody M11 and pyro A $\beta$ 11-40/42 specific antibody P82....To demonstrate the specificity of M11 and P82 for free and pyro A $\beta$ 11-40/42, respectively, synthetic A $\beta$ 11-40 and pyro A $\beta$ 11-40 peptides were used in Western blot and ELISA analyses...Thus, P82 specifically binds to pyro A $\beta$ 11-40/42 peptides whereas M11 specifically recognizes free A $\beta$ 11-40/42 peptides*". Clearly, the skilled artisan recognizes the claimed antibody specifically recognize the truncated A $\beta$ 11-x peptides and not the full-length A $\beta$ 1-40/42 and utilized the claimed antibody to investigate the role of the A $\beta$  species in the Alzheimer's disease. This clearly support that the claimed antibody has function, property and characteristics different from the art-disclosed antibody.

Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 102 are respectfully requested.

### **Rejections under 35 U.S.C. § 103**

Claims 17-25, 28 and 31-36 are rejected to under 35 U.S.C. § 103(a) for being unpatentable over Huse in view of Walker and WO01/62801.

As discussed above, all of the antibodies disclosed in Huse lack one or more properties of the claimed antibodies. None of the art provides motivation to modify the antibodies of Huse to arrive at the claimed antibodies.

One of the antibodies disclosed in Huse, BNT77, was produced using the A $\beta$ 11-16 immunogen (including the epitope of the claims) and binds N-terminal truncated (A $\beta$ 11-x) peptides. However, in contrast to the claimed antibodies, BNT77 also binds to full-length (A $\beta$ 1-40/42) A $\beta$  peptides. One of ordinary skill in the art, reading Huse, would not have been motivated to produce an antibody of the claims, since it flows from Huse that an antibody which could specifically bind to N-terminal truncated A $\beta$  peptides at one or more epitopes in the first 5-7 N-terminal amino acids would also specifically bind to full-length A $\beta$ 1-40/42 peptides. In fact, Huse teaches away from producing the claimed antibody, since it teaches that an antibody produced with the first 5 N-terminal amino acids of A $\beta$ 11-x would bind to full-length A $\beta$ 1-40/42 peptides.

Both Walker and WO01/62801 are silent as to whether the antibodies disclosed therein specifically bind to A $\beta$ 11-x peptides. The antibodies of both Walker and WO01/62801 bind to full length A $\beta$ 1-40/42 peptides. Therefore, they do not cure the deficiency in Huse.

Accordindgly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 103 are respectfully requested.

### **Rejections under 35 U.S.C. § 112**

Claims 18 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "binds to human A $\beta$ 11-x" and "binds to human A $\beta$ 11-x", respectively.

In response, Applicants amend claims 18 and 19 to recite "A $\beta$ 11-x polypeptide at one or more epitopes present on the first 5 to 7 N-terminal amino acids". Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph are respectfully requested.

**Allowable Subject Matter**

Applicants greatly appreciate the Office's indication that claims 26-27, 29 and 30 would be allowable if rewritten in independent form. As discussed above, Applicants believe that claims 17-36 are allowable and therefore request early consideration and prompt allowance of the pending claims. Should the office require anything further, it is invited to contact applicants' representative at the telephone number below.

Respectfully submitted,

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